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S9 Mitochondria and Neuronal Function

9L1

Different substrate supply mechanisms to mitochondria from astrocytes and neurons support astrocyte–neuron lactate shuttle hypothesis

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We have shown that glutamate- and α-glycerophosphate (α-GP)-dependent OXPHOS of isolated brain mitochondria is regulated by cytosolic Ca^{2+} (Ca^{2+}_{cyt}) [1,2] due to the activation of aralar and α-GPDH [3]. These enzymes are part of the malate aspartate shuttle (MAS) and of the α-GP-shuttle (α-GPS) [3]. Both shuttles are coupled with pyruvate formation from lactate [1]. Surprisingly we found in isolated brain mitochondria that α-GP activates the MAS. Therefore, we assume that neurons have no α-GPS but MAS only. Since astrocytes have no aralar [4] they have no MAS but α-GPS. To prove that, we investigated mitochondria isolated from astrocytes (AM) and compared them with those isolated of from brain (BM) containing neurons, astrocytes and other cells. Specific respiration rates of AM are much lower than that of BM. The ratio of state $3_{glu/pyr/mal}$/state $3_{G3P/suc}$ is 0.5 ± 0.1 in AM but 1.1 ± 0.12 in BM ($P<0.005$) indicating a strongly limited capacity to oxidize complex I dependent substrates in AM compared to BM. Moreover glutamate dependent respiration cannot be activated by Ca^{2+}_{cyt} in AM but in BM.

We assume that the missing MAS in astrocytes keeps the pyruvate concentration low in astrocytes since the NADH formed by GAPDH is mainly used for lactate formation. In principle the α-GPS could take over the role in NADH re-oxidation, but the low oxidation capacity of AM for complex I dependent substrates as well as the very low affinity of mitochondrial GPDH to α-GP will limit the mitochondrial pyruvate oxidation. This mechanism could explain the excessive lactate formation in astrocytes, and its export to neurons which have a large MAS capacity according to the astrocyte–neuron lactate shuttle hypothesis proposed by Pellerin [5].

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9L2

Mitochondrial quality control and neurodegeneration

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A dysfunction of mitochondria has severe cellular consequences and is linked to aging and neurodegeneration in human. Mitochondrial proteases emerge as central regulators that coordinate different quality control pathways within an interconnected network of mechanisms. A failure of this system causes neuronal loss in a steadily increasing number of neurodegenerative disorders. Whereas irreversibly damaged mitochondria can be selectively removed by autophagy, various intraorganellar proteases degrade non-native mitochondrial proteins and limit mitochondrial damage. These include hexameric *m*-AAA proteases, ATP-dependent proteases in the inner membrane of mitochondria, mutations of which are associated with hereditary spastic paraplegia and spinocerebellar ataxia (SCA28). *m*-AAA proteases are part of large supercomplexes with prohibitin scaffolds in the inner membrane, which are thought to generate functional membrane domains of a defined protein and phospholipid composition. Recent experiments link the function of *m*-AAA protease/prohibitin complexes to mitochondrial fusion and the processing of the dynamin-like GTPase OPA1, which is emerging as a central mechanism to monitor mitochondrial integrity. Mitochondrial depolarization causes the proteolytic breakdown of the dynamin-like GTPase OPA1 by the OMA1 peptidase in the inner membrane triggering mitochondrial fragmentation and the segregation of dysfunctional mitochondria. How a dysfunction of mitochondria is sensed and OMA1 activated is presently not understood, but studies on genes interacting with prohibitin scaffolds in yeast point to a crucial role of the phospholipid composition of mitochondrial membranes. Recent experiments on the role of this mitochondrial quality control mechanism for cell survival and neurodegeneration will be discussed.

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9L3

Parkin: A stress-protective E3 ubiquitin ligase maintaining mitochondrial integrity

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